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## Medical Policy



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**\*Current Policy Effective Date: 7/1/23**  
(See policy history boxes for previous effective dates)

### **Title: Genetic Testing for Retinal Dystrophies**

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#### **Description/Background**

##### **Description of Disease**

Retinal dystrophies are a heterogeneous group of diseases in which the retina degenerates, leading to either partial or complete blindness. The severe and hereditary forms, retinitis pigmentosa (RP) and various macular degenerations, affect approximately one in 3000 people, but many more suffer from aging macular dystrophy in later life. Patients with RP present with narrowing visual fields and night blindness, while those with diseases of the macula lose central vision first. These are heterogeneous disorders, with wide variation in severity, mode of inheritance and phenotype. However, with the widespread application of linkage analysis and mutation detection techniques, a complex underlying pathology has now been revealed. In total, 66 distinct non-overlapping genes or gene loci have been implicated in the various forms of retinal dystrophy, with more being reported regularly in the literature. Within the category of non-syndromic RP alone, there are at least 22 genes involved, with further allelic heterogeneity arising from different mutations in the same gene. This complexity presents a problem for those involved in counseling patients, and compounds the search for therapies. Nevertheless, several lines of research raise the hope of generic treatments applicable to all such patients, while the greater understanding of normal visual function that arises from genetic studies may open up new avenues for therapy.

##### **Clinical Diagnosis**

##### **Retinitis Pigmentosa (RP) (81400, 81404, 81408, 81434, 81479)**

Retinitis pigmentosa (RP) is the most commonly seen hereditary retinal disease that can have a common phenotypic presentation. RP can occur alone or as part of a syndrome, such as Ushers syndrome, in which hearing loss is associated with retinal degeneration. RP affects about one in 3,500 people worldwide. In the United States, approximately 100,000 people are affected.

The classic symptoms of RP are night-blindness, which can occur at any age depending on the type of RP and peripheral visual field loss. Clinical findings are sometimes unclear; the most consistent finding in RP is arteriolar attenuation. Other findings can include bone-spicule pigmentation; a grayish retinal sheen; pale, waxy disc, sometimes with drusen; cystoids macular edema; and posterior subcapsular cataract. Visual field testing initially will show a ring scotoma in the mid-periphery. Diagnosis is most often made based on the patient's symptoms, the clinical picture, visual fields and specialized electrodiagnostic testing.

### **Leber Congenital Amaurosis (LCA) (81404, 81406, 81408, 81434, 81479)**

Leber congenital amaurosis affects about 5,000 children in the United States. These children present with nystagmus and severe visual impairment. Clinical findings include a fundus that is normal early on but eventually acquires a degenerative or mottled appearance. The diagnostic hallmark test result of this disease is a markedly abnormal or flat electroretinogram (ERG).

### **Stargardt Disease (Fundus Flavimaculatus) (81408, 81479)**

Stargardt disease is a hereditary disease that affects the macula in young patients. Prevalence is estimated to be between one in 8,000 and one in 10,000. The typical patient presents with a gradual loss of central vision. Early on, the fundus can look almost normal. Often there is macular granularity that can progress to cause a metallic or beaten-bronze appearance. Many patients also manifest deep yellowish fishtail or pisciform flecks and some have flecks with no maculopathy. Color vision may be normal or mildly reduced as is the ERG.

### **Other Retinopathies (81408, 81404, 81434)**

Mutations in the *ABCA4* gene are also responsible for cone-rod dystrophy (a group of diseases that affect the cones and central vision first and then the rods, the opposite of RP). This dystrophy causes reduced vision and color vision loss and eventually night vision problems. Clinically the fundus can look normal or can have macular changes. The presences of multiple mutations in the *ABCA4* gene are also responsible for some forms of RP. There are cases in which one member of the patient's family has Stargardt disease and a close relative has RP.

### **Treatment**

For most inherited eye diseases, no effective treatments exist. Although gene- and autologous cell-based treatment approaches have shown great promise in the laboratory, the speed with which gene discoveries have progressed to clinical trials has been slow. Stem cell technology has created the opportunity to advance treatments for multiple forms of blindness. Researchers are now able to use a person's cells to generate tissues found in the eye. This technology can be used to explain the genetic causes of disease and develop personalized treatment strategies.

### **Gene Mutations**

Few Mendelian disorders exhibit the degree of genetic heterogeneity demonstrated by RP, one of the most common retinal dystrophies, with a worldwide prevalence of 1 in 4,000. Over 100 genes have been associated with this condition. Moreover, other retinal dystrophies, including cone-rod dystrophy (CRD), cone dystrophy, and Stargardt disease, also exhibit genetic heterogeneity. Inherited retinal dystrophies demonstrate significant phenotypic heterogeneity. For example, mutations in the *ABCA4* gene (OMIM 601691) have been associated with several distinct hereditary retinal dystrophies and can have highly variable retinal appearance on clinical examination, ranging from normal to widespread pigmentary changes (Stargardt disease, CRD, cone dystrophy, and RP).<sup>1</sup> The usual diagnostic approach has been to use array-based primer extension (APEX) technology or Sanger sequencing to examine specific

mutations, exons or gene targets. These techniques are reported to have a diagnostic yield of approximately 10-20% in RD patients. There are currently few treatment options for these patients.<sup>2</sup>

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## Regulatory Status

No U.S. Food and Drug Administration (FDA)-cleared genotyping tests were found. The U.S. Food and Drug Administration (FDA) has not regulated these tests to date. Thus, genotyping is offered as a laboratory-developed test. Clinical laboratories may develop and validate tests in-house (“home-brew”) and market them as a laboratory service; such tests must meet the general regulatory standards of the Clinical Laboratory Improvement Act (CLIA).

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## Medical Policy Statement

Genetic testing in patients with retinal dystrophy for biallelic *RPE65* mutation is established in patients who are eligible for Voretigene Neparvovec-rzyl also known as *SPK-RPE65* gene therapy.

The peer reviewed medical literature has not demonstrated the clinical utility of general genetic testing for retinal dystrophies. Therefore, this service is experimental/investigational.

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## Inclusionary and Exclusionary Guidelines

Criteria for biallelic *RPE65* mutation testing:

- Visual acuity of 20/60 or worse in both eyes, or
- Binocular visual field less than 20 degrees in any meridian, and
- Retinal thickness of >100 microns within the posterior pole

All requests must be supported by submission of chart notes and patient specific documentation.

Please reference pharmacy policy for Voretigene Neparvovec.

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**CPT/HCPCS Level II Codes** *(Note: The inclusion of a code in this list is not a guarantee of coverage. Please refer to the medical policy statement to determine the status of a given procedure.)*

### Established codes:

81406

### Other codes (investigational, not medically necessary, etc.):

81401

81404

81405

81407

81408

81434

81479

## Rationale

### Literature Search

Making a specific diagnosis of a retinal dystrophy based on pattern recognition alone might not be possible as disease conditions with different genetic causes have near-similar clinical features. Genetic testing may be helpful in confirming a diagnosis.<sup>3</sup> Options for genetic testing in patients with Inherited Retinal Dystrophies (IRDs) are numerous. Clinically available molecular testing for retinal disorders are listed in Table 1.

**Table 1. Molecular Testing for Retinal Disorders<sup>4</sup>**

Type of Test	Indication	Turnaround Time (weeks)	Approx. Cost <sup>a</sup>
Single site testing	<ul style="list-style-type: none"><li>Familial mutation(s) is known</li></ul>	2-3	\$120-\$500
Sanger sequencing	<ul style="list-style-type: none"><li>Clinical diagnosis of a monogenic disorder</li></ul>	3-6	\$200-\$2,000 <sup>b</sup>
Chromosomal SNP microarray	<ul style="list-style-type: none"><li>Clinical suspicion of syndromic retinopathy</li></ul>	1-4	\$2,500
Mitochondrial genome sequencing	<ul style="list-style-type: none"><li>Clinical suspicion of an unknown mitochondrial syndrome</li></ul>	7-8	≈\$3,000
Disease-specific Sanger sequencing or NGS gene panels	<ul style="list-style-type: none"><li>Clinical diagnosis of a heterogeneous disorder</li></ul>	6-12	\$300-\$4,000 <sup>c</sup>
Array CGH deletion / duplication panels	<ul style="list-style-type: none"><li>Clinical diagnosis of a heterogeneous disorder</li><li>Ordered in conjunction with or after negative NGS panels</li></ul>	2-4	\$650-\$1,300
Comprehensive NGS retina gene panel	<ul style="list-style-type: none"><li>Clinical diagnosis of a heterogeneous disorder</li><li>Uncertain diagnosis</li></ul>	12	≈\$2,500
Whole-exome sequencing	<ul style="list-style-type: none"><li>Clinical diagnosis of a heterogeneous disorder</li><li>Uncertain diagnosis</li><li>Negative findings on previous NGS</li></ul>	12-24	\$5000-\$7,000 <sup>d</sup>

Ar, autosomal recessive; CGH, comparative genomic hybridization; NGS, next-generation sequencing; SNP, single-nucleotide polymorphism.

<sup>a</sup>The "approximate cost" was derived by surveying four to seven laboratories offering each specific test to provide a frame of reference.

Clinicians should consult laboratory personnel or websites for up-to-date pricing.

<sup>b</sup>Price variation largely reflects the number of exons required to sequence.

<sup>c</sup>Price variation largely reflects the number of genes analyzed in a Sanger sequencing or NGS panel.

<sup>d</sup>Price estimations are for proband-only testing.

To determine the efficacy of multiple versions of a commercially available arrayed primer extension (APEX) microarray chip for autosomal recessive retinitis pigmentosa (arRP), Van Huet et al studied 250 patients suspected of arRP who were genetically analyzed with the APEX microarray.<sup>5</sup> The mode of inheritance was autosomal recessive according to the pedigree (including isolated cases). If the microarray identified a heterozygous mutation, a Sanger sequencing of exons and exon/intro boundaries of the specific gene was performed. The efficacy of this microarray chip with the additional Sanger sequencing approach was determined by the percentage of patients that received a molecular diagnosis. Data was also

collected from genetic tests other than the APEX analysis for arRP to provide a detailed description of the molecular diagnoses in this study cohort.

The APEX microarray chip for arRP identified the molecular diagnosis in 21 (8.5%) of the patients in this cohort. Additional Sanger sequencing yielded a second mutation in 17 patients (6.8%), thereby establishing the molecular diagnosis. In total, 38 patients (15.2%) received a molecular diagnosis after analysis using the microarray and additional Sanger sequencing approach. The authors concluded that the efficacy of the commercially available APEX microarray chips for arRP appears to be low, most likely caused by the limitations of this technique and the genetic and allelic heterogeneity of RP.

In a retrospective case series, Westeneng-van Haften et al, describe the genotype and phenotype of patients with a late-onset Stargardt's disease (STGD1).<sup>6</sup> Twenty-one unrelated STGD1 patients with an age at onset of  $\geq 45$  years and  $\geq 1$  rare variant in the *ABCA4* gene underwent ophthalmologic examination, including best-corrected visual acuity (BCVA), Amsler grid testing, fundus photography, fluorescein angiography (FA), spectral-domain optical coherence tomography (OCT), fundus autofluorescence (FAF) imaging, full-field electroretinography (ERG), multifocal ERG, and central visual field testing. Analysis of the *ABCA4* gene was performed using microarray analysis, sequencing, and multiplex ligation-dependent probe amplification. In addition, the *PRPH2* and *CFH* genes were sequenced. Outcome measures include age at onset, BCVA, fundus appearance, FA, FAF, and OCT findings; *ABCA4* mutations; and genotype-phenotype correlation.

The mean age at onset was 55 years (range, 45-72 years). Seven patients were diagnosed without visual symptoms (age range, 45-83 years). The BCVA was  $\geq 20/40$  in 24 eyes of 14 patients (59%) owing to foveal sparing. On ophthalmoscopy, late-onset STGD1 showed flavimaculatus flecks (15 patients), small flecks surrounding mottled foveal changes (3 patients), extensive chorioretinal atrophy (2 patients), or small yellowish spots in the macular (1 patient). The fundus flecks showed increased autofluorescence on FAF. The choroidal background fluorescence on FA was obscured in 16 patients (80%). A single heterozygous *ABCA4* variant was found in 11 patients (52%), 2 compound heterozygous variants in 8 patients (38%), and a homozygous variant in 2 patients (10%). No *PRPH2* or *CFH* mutations were detected. The authors concluded that late-onset STGD1 is at the mild end of the spectrum of retinal dystrophies caused by *ABCA4* mutations. The BCVA is frequently preserved in late-onset STGD1 patients owing to foveal sparing. This phenotype may be caused by one or two *ABCA4* variants. The differential diagnosis between late-onset STGD1 and age-related macular degeneration may be challenging. A thorough clinical and genetic analysis makes a distinction possible.

Mutations in the *ABCA4* gene are heterogeneous and somewhat ethnic specific and can result in autosomal recessive Stargardt disease (STGD1), cone or cone-rod dystrophy (CRD), and retinitis pigmentosa. Jiang and colleagues recruited 161 Chinese patients for genetic analysis; these included 96 patients diagnosed with Stargardt disease (STGD1) and 65 individuals with Cone-rod dystrophy (CRD).<sup>7</sup> All patients underwent ophthalmic examinations. All coding exons and exon/intron boundaries of the *ABCA4* gene were screened for mutations by PCR-based DNA sequencing, followed by analyses for pathogenicity by in silico programs. At least two diseases causing *ABCA4* alleles in 102 unrelated patients (63.4%), one disease-causing allele in 16 patients (9.9%), and no disease-causing allele in 43 affected individuals (26.7%), giving an overall mutation detection rate of 73.3% (118/161). In total, 136 disease-causing variants of the *ABCA4* gene, including 85 novel ones, were identified. The authors

concluded that the mutation spectrum of the *ABCA4* gene in Chinese patients was quite different from that of Caucasian patients.

Oishi et al performed comprehensive molecular testing in 329 Japanese RP and Usher syndrome patients by using a custom capture panel that covered the coding exons/intron boundaries of all 193 known inherited eye disease genes combined with Illumina HiSeq 2500.<sup>8</sup> Candidate variants were screened using systematic data analysis, and their potential pathogenicity was assessed according to the frequency of the variants in normal populations, in silico prediction tools (computer simulation), and compatibility with known phenotypes or inheritance patterns. Causative mutations were detected in 12 patients (27.9%). In total, 14 distinct mutations were identified in the genes *ABCA4*, *CDHR1*, *CRB1*, *CRX*, *GUCY2D*, *KCNV2*, *PROM1*, *PRPH2*, and *RDH5*. The authors concluded that targeted exome sequencing effectively identified causative mutations in Japanese patients with cone dystrophy or cone-rod dystrophy. The results confirmed the heterogeneity of the genes responsible.

Perez-Carro et al analyzed a cohort of 47 unrelated Spanish families pre-classified as autosomal recessive or isolated RP.<sup>9</sup> An in-house gene panel comprising of 75 known RP genes was used for analysis. Disease-causing mutations were found in 27 out of 47 cases achieving a mutation detection rate of 57.4%. In total, 33 pathogenic mutations were identified, 20 of which were novel mutations (60.6%). Furthermore, not only single nucleotide variations but also copy-number variations, including three large deletions in the *USH2A* and *EYS* genes, were identified. Finally, seven out of 27 families, displaying mutations in the *ABCA4*, *RP1*, *RP2*, and *USH2A* genes, could be genetically or clinically reclassified. The authors concluded that these results demonstrate the potential of panel-based NGS strategy in RP diagnosis.

Ellingford and colleagues compared the efficacy of whole genome sequencing (WGS) with targeted next-generation sequencing (NGS) in the diagnosis of inherited retinal disease (IRD).<sup>10</sup> The authors retrospectively reviewed the findings from a diagnostic NGS DNA test for 562 patients with IRD. A subset of 46 of 562 patients also underwent WGS, and they compared mutation detection rates and molecular diagnostic yields. In addition, they compared the sensitivity and specificity of the 2 techniques to identify known single nucleotide variants (SNVs) using 6 control samples with publicly available genotype data.

Across known disease-causing genes, targeted NGS and WGS achieved similar levels of sensitivity and specificity for SNV detection. However, WGS also identified 14 clinically relevant genetic variants that had not been identified by NGS diagnostic testing for the 46 individuals with IRD. Identification of these variants confirmed a molecular diagnosis of IRD for 11 of the 33 individuals referred for WGS who had not obtained a molecular diagnosis through targeted NGS testing. Weighted estimates, accounting for population structure, suggest that WGS methods could result in an overall 29% (95% confidence interval, 15-45) uplift in diagnostic yield. The authors concluded that WGS methods can detect disease-causing genetic variants missed by current NGS diagnostic methodologies for IRD.

Liu et al postulated that genetic evaluations of patients with IRD might result in better clinical assessments and better management of patients.<sup>11</sup> A cohort of 20 Chinese families affected with autosomal recessive IRD were recruited. To identify disease-causing mutations in the patients, the targeted sequence capture of IRD-relevant genes using two in-house-designed microarrays, followed by NGS, was performed. Bioinformatics annotation, intrafamilial cosegregation analysis, in silico analyses, and functional analyses were subsequently

conducted for the variants identified by NGS. Homozygous and biallelic variants were identified in 11 of the 20 families (55%) as very likely disease-causing mutations, including a total of 17 alleles, of which 12 are novel. The 17 alleles identified here include 3 missense, 6 nonsense, 4 frameshift, and 4 splice site mutations. In addition, we found biallelic RP1 mutations in a patient with cone-rod dystrophy, which was not previously correlated with RP1 mutations. Moreover, the identification of pathogenic mutations in 3 families helped to refine their clinical diagnoses. The authors concluded that genetic evaluations with targeted NGS might result in a better clinical diagnosis and better clinical assessment.

Fujinami et al applied NGS strategy for screening the *ABCA4* gene in a British cohort with *ABCA4*-associated disease.<sup>12</sup> They identified 79 patients with a clinical diagnosis of *ABCA4*-associated disease who had a single variant identified by the *ABCA4* microarray. Comprehensive phenotypic data were obtained, and the NGS strategy was applied to identify the second allele by means of sequencing the entire coding region and adjacent intronic sequences of the *ABCA4* gene. Identified variants were confirmed by Sanger sequencing and assessed for pathogenicity by in silico analysis.

Of the 42 variants detected by prescreening with the microarray, in silico analysis suggested that 34, found in 66 subjects, were disease-causing and 8, found in 13 subjects, were benign variants. We detected 42 variants by NGS, of which 39 were classified as disease-causing. Of these 39 variants, 31 were novel, including 16 missense, 7 splice-site-altering, 4 nonsense, 1 in-frame deletion, and 3 frameshift variants. Two or more disease-causing variants were confirmed in 37 (47%) of 79 patients, one disease-causing variant in 36 (46%) subjects, and no disease-causing variant in 6 (7%) individuals. The authors concluded that the application of the NGS platform for *ABCA4* screening enabled detection of the second disease-associated allele in approximately half of the patients where one mutation had been detected with the APEX array.

In another case series, Riveiro-Alvarez et al assessed genotype-phenotype correlation and disease progression in 10 years by considering the type of variants and age at onset of autosomal recessive retinal disorders including Stargardt's disease (arSTGD), cone-rod dystrophy (arCRD) and retinitis pigmentosa (arRP).<sup>13</sup> A total of 420 unrelated Spanish families were analyzed through a combination of *ABCR400* genotyping microarray, denaturing high-performance liquid chromatography, and high-resolution melting scanning. Direct sequencing was used as a confirmation technique for the identified variants. Screening by multiple ligation probe analysis was used to detect possible large deletions or insertions in the *ABCA4* gene. Selected families were analyzed further by next generation sequencing.

Overall, the authors detected 70.5% and 36.6% of all expected *ABCA4* mutations in arSTGD and arCRD patient cohorts, respectively. In the fraction of the cohort where the *ABCA4* gene was sequenced completely, the detection rates reached 73.6% for arSTGD and 66.7% for arCRD. However, the frequency of possibly pathogenic *ABCA4* alleles in arRP families was only slightly higher than that in the general population. Moreover, in some families, mutations in other known arRP genes segregated with the disease phenotype. The authors concluded that an increasing understanding of causal *ABCA4* alleles in arSTGD and arCRD facilitates disease diagnosis and prognosis and also is paramount in selecting patients for emerging clinical trials of therapeutic interventions. Because *ABCA4*-associated diseases are evolving retinal dystrophies, assessment of age at onset, accurate clinical diagnosis, and genetic testing are important. They suggest that *ABCA4* mutations may be associated with a retinitis pigmentosa-like phenotype often as a consequence of severe (null) mutations, in cases of

long-term, advanced disease, or both. Patients with classical arRP phenotypes, especially from the onset of the disease, should be screened first for mutations in known arRP genes and not *ABCA4*.

Miraldi et al, conducted a retrospective, cross-sectional study of 112 patients with Stargardt disease.<sup>14</sup> The study evaluated the correlation between age at presentation, best-corrected visual acuity (BCVA), and *ABCA4* genotypes. Mean age at presentation was  $30 \pm 16$  years (range 6-78 years) for the 112 patients of 104 families. Ninety-eight or 90 families had a probable molecular diagnosis. The authors found BCVA is not related to age of presentation in a linear or polynomial manner; that BCVA of patients presenting in the first decade was significantly worse than those presenting in later decades ( $p=0.04$ ); that patients who harbored two or more mutations presented earlier and had worse BCVA than those with no or 1 mutation identified by any method of testing ( $n=112$ ,  $p=3.29 \times 10^{-6}$ ) or by full sequencing ( $n=32$ ,  $p=0.02$ ); that 16 patients with c.5882G>A allele demonstrated better BCVA than the remaining patients ( $p=0.01$ ); and that 10 patients with the c.5461-10T>C mutation presented earlier ( $p=0.02 \times 10^{-5}$ ) and had more severe disease. Epidemiological and genotypical findings indicate visual prognosis in patients with Stargardt disease. The authors concluded that the present data may help in assessing patients for emerging therapies.

Lee et al assess the diagnostic yield and the practicality of implementing whole exome sequencing (WES) within a clinical ophthalmology setting.<sup>1</sup> Twenty-six patients with a variety of presumed hereditary retinal dystrophies were enrolled during clinical appointment in a university-based ophthalmic genetics clinic. Participants were offered WES in addition to clinically available sequencing gene panels to determine the molecular etiology of their retinal dystrophy. Twenty-six of 29 eligible patients opted to undergo molecular testing. Each participant chose WES in addition to, or in lieu of, sequencing gene panels. WES successfully identified known pathogenic mutations of suspected deleterious variants in 57.7% of participants. Additionally, one participant had two autosomal dominant medically actionable incidental findings (unrelated to retinopathy) that were reported to enable the participant to take preventive action and reduce risk for future disease. The authors concluded that more than half of all participants had an identified molecular etiology.

### **Gene and Cell Therapy**

According to Ehmann and colleagues, significant progress has brought stem cell therapy from proof-of-concept animal models to human clinical trials.<sup>15,16</sup> Although in its infancy, valuable safety and efficacy data are starting to emerge from trials looking at cell therapies from age-related macular degeneration, Stargardt's macular dystrophy, retinitis pigmentosa and other ischemic retinopathies.

Ocular gene therapy involves the introduction of an exogenous gene product to a host's cellular and genetic machinery for endogenous production of a desired gene product. The eye represents an ideal target organ due to its easy visibility and accessibility, and several trials have demonstrated proof-of-principle safety and efficacy in a subtype of Leber's congenital amaurosis. There are numerous ongoing clinical trials exploring gene therapy in other retinal diseases. In autosomal recessively inherited retinal degenerations, the introduced gene product replaces a known genetically deficient gene product and provides restoration of function. In other disease states, such as neovascular age-related macular degeneration, the delivered gene product modulates existing proteins within a cell, such as vascular endothelial growth factor, for a desired therapeutic effect. This latter approach may have broader



applications in other diseases such as diabetes and other retinal vascular disease that are as yet unrealized.<sup>17-19</sup>

Russell et al (2017) reported on a phase 3 trial on the safety and efficacy of voretigene neparvovec (AAV2-hRPE65v2).<sup>20</sup> In this open-label, randomized, controlled phase 3 trial done at two sites in the USA, individuals aged 3 years or older with, in each eye, best corrected visual acuity of 20/60 or worse, or visual field less than 20 degrees in any meridian, or both, with confirmed genetic diagnosis of biallelic RPE65 mutations, sufficient viable retina, and ability to perform standardized multi-luminance mobility testing (MLMT) within the luminance range evaluated, were eligible. Participants were randomly assigned (2:1) to intervention or control using a permuted block design, stratified by age (<10 years and ≥10 years) and baseline mobility testing passing level (pass at ≥125 lux vs. <125 lux). Graders assessing primary outcome were masked to treatment group. Intervention was bilateral, subretinal injection of  $1.5 \times 10^{11}$  vector genomes of voretigene neparvovec in 0.3 mL total volume. The primary efficacy endpoint was 1-year change in MLMT performance, measuring functional vision at specified light levels. The intention-to-treat (ITT) and modified ITT populations were included in primary and safety analyses. Thirty-one individuals were enrolled and randomly assigned to intervention (n=21) or control (n=10). One participant from each group withdrew after consent, before intervention, leaving an mITT population of 20 intervention and nine control participants. At 1 year, mean bilateral MLMT change score was 1.8 (SD 1.1) light levels in the intervention group versus 0.2 (1.0) in the control group (difference of 1.6, 95% CI 0.72-2.41, p=0.0013). Thirteen (65%) of 20 intervention participants, but no control participants, passed MLMT at the lowest luminance level tested (1 lux), demonstrating maximum possible improvement. No product-related serious adverse events or deleterious immune responses occurred. Two intervention participants, one with a pre-existing complex seizure disorder and another who experienced oral surgery complications, had serious adverse events unrelated to study participation. Most ocular events were mild in severity. The authors concluded that voretigene neparvovec gene replacement improved functional vision in RPE65-mediated inherited retinal dystrophy previously medically untreatable.

Le Meur et al (2018) evaluated the safety and efficacy of unilateral subretinal injection of the adeno-associated vector (AAV) serotypes 2 and 4 RPE65-RPE65 vector in patients with Leber congenital amaurosis (LCA) associated with *RPE65* gene deficiency.<sup>21</sup> We evaluated ocular and general tolerance and visual function up to 1 year after vector administration in the most severely affected eye in nine patients with retinal degeneration associated with mutations in the *RPE65* gene. Patients received either low ( $1.22 \times 10$  to  $2 \times 10$  vector genomes [vg]) or high (between  $3.27 \times 10$  and  $4.8 \times 10$  vg) vector doses. An ancillary study, in which six of the original nine patients participated, extended the follow-up period to 2-3.5 years. All patients showed good ophthalmological and general tolerance to the rAAV2/4-RPE65-RPE65 vector. We observed a trend toward improved visual acuity in patients with nystagmus, stabilization and improvement of the visual field, and cortical activation along visual pathways during fMRI analysis. OCT analysis after vector administration revealed no retinal thinning, except in cases of macular detachment. The findings show that the rAAV2/4-RPE65. *RPE65* vector was well tolerated in nine patients with *RPE65*-associated LCA. Efficacy parameters varied between patients during follow-up.

## Optogenetics

Optogenetics combines genetic strategies that target light sensitive proteins within the cells and optical stimulation to activate these selectively targeted proteins. To restore useful vision in blind patients, optogenetics takes advantages of two facts: (1) Even after the occurrence of

blindness caused by IRD, many cone photoreceptors survive and maintain their cell body for extended periods; and (2) the remarkable proteins channelrhodopsin-2 and halorhodopsin function as light gated ion channels. The key goal of optogenetic vision restoration is to convert strategically important retinal cell types into “artificial photoreceptors.”<sup>22</sup>

## Retinal Prosthetics

In IRDs, parts of the inner retina survive even after complete degeneration of the retinal photosensitive layer and remain responsive to electrical stimulation even in the late stages of the disease. Visual neuroprosthetics use electrical stimulation to activate the remaining inner retinal network, allowing these cells to take over the function of the lost photoreceptors. Different groups are currently working on retinal implant devices. The longest and largest follow up data at present are reported for the implant Argus II, made by the U.S. company Second Sight Medical Products. This device is positioned on the surface of the retina. It communicates directly with the ganglion and bipolar cells, receiving light signals from an external camera system. Argus II received the first-ever commercial use approval for a retinal prosthesis device to treat adult patients with retinal degenerative diseases such as RP.<sup>22</sup>

## ONGOING AND UNPUBLISHED CLINICAL TRIALS

Some currently unpublished trials that might influence this review are listed in Table 2.

**Table 2: Summary of Key Trials**

NCT No.	Trial Name	Planned Enrollment	Completion Date
<b>Ongoing</b>			
NCT04123626 <sup>a</sup>	A Prospective First-In-Human Study to Evaluate the Safety and Tolerability of QR-1123 in Subjects With Autosomal Dominant Retinitis Pigmentosa (adRP) Due to the P23H Mutation in the RHO Gene (AURORA)	11	Jun 2022 (ongoing)
NCT03913143 <sup>a</sup>	Double-masked, Randomized, Controlled, Multiple-dose Study to Evaluate Efficacy, Safety, Tolerability and Syst. Exposure of QR-110 in Leber's Congenital Amaurosis (LCA) Due to c.2991+1655A>G Mutation (p.Cys998X) in the CEP290 Gene (ILLUMINATE)	36	Mar 2023 (ongoing)
NCT02946879 <sup>a</sup>	Long-term Follow-up Study of Participants Following an Open-Label, Multi-centre, Phase I/II Dose Escalation Trial of an Adeno-associated Virus Vector (AAV2/5-OPTIRPE65) for Gene Therapy of Adults and Children With Retinal Dystrophy Owing to Defects in RPE65 (LCA2)	27	Apr 2023 (ongoing)
NCT04671433 <sup>a</sup>	Phase 3 Randomized, Controlled Study of AAV5-RPGR for the Treatment of X-linked Retinitis Pigmentosa Associated With Variants in the RPGR Gene	66	Oct 2023 (recruiting)
NCT03872479 <sup>a</sup>	Open-Label, Single Ascending Dose Study to Evaluate the Safety, Tolerability, and Efficacy of AGN-151587 (EDIT-101) in Adult and Pediatric Participants With Leber Congenital Amaurosis Type 10 (LCA10), With Centrosomal Protein 290 (CEP290)-Related Retinal Degeneration Caused by a Compound Heterozygous or Homozygous Mutation Involving c.2991+1655A>G in Intron 26 (IVS26) of the CEP290 Gene ("LCA10-IVS26")	34	Mar 2024 (recruiting)
NCT03597399 <sup>a</sup>	A Post-Authorization, Multicenter, Longitudinal, Observational Safety Registry Study for Patients Treated With Voretigene Neparvovec in US	87	Jun 2025 (ongoing)

<b>NCT No.</b>	<b>Trial Name</b>	<b>Planned Enrollment</b>	<b>Completion Date</b>
NCT02317887	A Phase I/IIa Study of RS1 Ocular Gene Transfer for X-linked Retinoschisis	12	Jul 2025 (ongoing)
NCT03328130 <sup>a</sup>	Safety and Efficacy of a Unilateral Subretinal Administration of HORA-PDE6B in Patients With Retinitis Pigmentosa Harboring Mutations in the PDE6B Gene Leading to a Defect in PDE6 $\beta$ Expression	17	Dec 2026 (ongoing)
NCT03326336 <sup>a</sup>	A Phase 1/2a, Open-Label, Non-Randomized, Dose-Escalation Study to Evaluate the Safety and Tolerability of GS030 in Subjects With Retinitis Pigmentosa (PIONEER)	15	Dec 2025 (recruiting)
NCT04516369 <sup>a</sup>	An Open-Label, Single-Arm Study to Provide Efficacy and Safety Data of Voretigene Neparvovec Administered as Subretinal Injection in Japanese Patients With Biallelic RPE65 Mutation-associated Retinal Dystrophy	4	May 2026 (ongoing)
NCT03316560 <sup>a</sup>	An Open-Label Dose Escalation Study to Evaluate the Safety and Efficacy of AGTC-501 (rAAV2tYF-GRK1-RPGR) in Subjects With X-linked Retinitis Pigmentosa Caused by RPGR Mutations	42	Aug 2026 (recruiting)
NCT03597399 <sup>a</sup>	A Post-Authorization, Multicenter, Longitudinal, Observational Safety Registry Study for Patients Treated With Voretigene Neparvovec	87	Jan 2025 (ongoing)
NCT00481546	Phase I Trial of Ocular Subretinal Injection of a Recombinant Adeno-Associated Virus (rAAV2-CBSB-hRPE65) Gene Vector to Patients With Retinal Disease Due to RPE65 Mutations (Clinical Trials of Gene Therapy for Leber Congenital Amaurosis) (LCA)	15	Jun 2026 (ongoing)
NCT04794101 <sup>a</sup>	Follow-up Phase 3 Randomized, Controlled Study of AAV5-RPGR for the Treatment of X-linked Retinitis Pigmentosa Associated With Variants in the RPGR Gene	66	Oct 2028 (recruiting)
NCT04517149 <sup>a</sup>	An Open-Label, Phase 1/2 Trial of Gene Therapy 4D-125 in Males With X-linked Retinitis Pigmentosa (XLRP) Caused by Mutations in the RPGR Gene	43	May 2029 (recruiting)
NCT00999609 <sup>a</sup>	A Safety and Efficacy Study in Subjects With Leber Congenital Amaurosis (LCA) Using Adeno-Associated Viral Vector to Deliver the Gene for Human RPE65 to the Retinal Pigment Epithelium (RPE) [AAV2-hRPE65v2-301]	31	Jul 2029 (ongoing)
NCT03602820 <sup>a</sup>	A Long-Term Follow-Up Study in Subjects Who Received an Adenovirus-Associated Viral Vector Serotype 2 Containing the Human RPE65 Gene (AAV2-hRPE65v2, Voretigene Neparvovec-rzyl) Administered Via Subretinal Injection	41	Jun 2030 (ongoing)
NCT01208389 <sup>a</sup>	A Follow-On Study to Evaluate the Safety of Re-Administration of Adeno-Associated Viral Vector Containing the Gene for Human RPE65 [AAV2-hRPE65v2] to the Contralateral Eye in Subjects With Leber Congenital Amaurosis (LCA) Previously Enrolled in a Phase 1 Study	12	Jun 2030 (ongoing)
NCT02435940	Foundation Fighting Blindness Registry, My Retina Tracker	20,000	Jun 2037 (recruiting)
<b>Unpublished</b>			
NCT03780257 <sup>a</sup>	A First-in-Human Study to Evaluate the Safety and Tolerability of QR-421a in Subjects With Retinitis Pigmentosa (RP) Due to Mutations in Exon 13 of the USH2A Gene (STELLAR)	20	Oct 2021 (completed)

NCT No.	Trial Name	Planned Enrollment	Completion Date
NCT03252847 <sup>a</sup>	An Open-Label, Multi-centre, Phase I/II Dose Escalation Trial of a Recombinant Adeno-associated Virus Vector (AAV2-RPGR) for Gene Therapy of Adults and Children With X-linked Retinitis Pigmentosa Owing to Defects in Retinitis Pigmentosa GTPase Regulator (RPGR)	49	Nov 2021 (completed)

NCT: national clinical trial.

<sup>a</sup> Denotes industry-sponsored or cosponsored trial.

## SUMMARY OF EVIDENCE

Retinal dystrophies are a group of heterogeneous conditions caused by numerous genes, many of which have almost the same clinical picture, a phenomenon known as genetic heterogeneity. Methods include targeted mutation analysis, microarray panels of all known mutations, complete sequencing of a specific gene or simultaneous sequencing of many exons. Although genetic testing strategies for inherited retinal dystrophies are changing radically, making testing possible for the majority of affected patients and families, the potential benefits and harms of such testing have yet to be clearly defined. All tests are not yet 100% sensitive, a negative or normal test result does not always mean a wrong diagnosis or absence of disease. Testing is also not 100% specific, a positive test (variation) does not always mean a mutation. More research is needed to analyze the significance of results and estimate the probability of the change being pathogenic.

Presymptomatic or predictive testing is particularly useful if timely medical benefits are associated with early awareness of the disease condition. However, with retinal dystrophy this is not the case, because in the majority of retinal dystrophies, preventive therapy is unknown. Still, genetic testing may assist individuals in making informed choices regarding education, employment, lifestyle and family planning.

For most IRDs, there is no effective treatment that can prevent or reverse vision loss. General recommendations include supportive measures to maintain the activities of daily living and improve quality of life. Gene therapy, a strategy to correct the genetic defects using viral or non-viral vectors, is currently available and can achieve definitive treatment by replacing or silencing a causative gene. Among many clinical trials of gene therapy for hereditary retinal diseases, a phase 3 clinical trial of voretigene neparvovec (AAV2-hRPE65v2, Luxturna) showed significant efficacy for *RPE65*-mediated inherited retinal dystrophy including Leber congenital amaurosis and RP.

Active research is being conducted to develop innovative treatments that address different aspects of the disease. These therapies aim to efficiently stop disease progression or restore some visual perception through retinal prosthesis, optogenetics, cell based therapies and sensory substitution devices.

## SUPPLEMENTAL INFORMATION

### PRACTICE GUIDELINES AND POSITION STATEMENTS

#### **American Academy of Ophthalmology (AAO)<sup>23</sup>**

According to the AAO's 2016 recommendations on clinical assessment of patients with inherited retinal degenerations (IRD), "Genetic testing plays an important role in improving the accuracy of diagnosis and prognosis, providing patients and families with specific inheritance risks, and guiding treatment decisions. For example, clinical trials of gene therapies for multiple genetic forms of IRD are in progress, and positive results have been reported from several of these studies."

#### **National Institute for Health and Care Excellence<sup>24</sup>**

In 2019, the National Institute for Health and Care Excellence published guidance for the use of voretigene neparvovec (Luxturna) in the treatment of inherited retinal dystrophies caused by *RPE65* gene mutations. The treatment is recommended for individuals with vision loss caused by inherited retinal dystrophy from confirmed biallelic *RPE65* mutations who have sufficient viable retinal cells. Despite uncertainty surrounding long-term durability, the committee felt this intervention is likely to provide important clinical benefits for individuals afflicted with inherited retinal dystrophies.

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### **Government Regulations**

#### **National:**

There is no national coverage determination specific to genetic testing for retinal diseases.

#### **Local:**

**Local Coverage Determination: Voretigene Neparvovec-rzyl (Luxturna®), L37863, for services on or after 05/28/2020.<sup>25</sup>**

This Local Coverage Determination (LCD) addresses limited indications of the gene therapy, [voretigene neparvovec-rzyl \(LUXTURNA®\)](#). Voretigene neparvovec-rzyl will be considered reasonable and necessary for the following inherited retinal degenerations with confirmed biallelic RPE65 mutations:

- Retinitis pigmentosa
- Leber congenital amaurosis

This limited coverage of voretigene neparvovec-rzyl (**LUXTURNA®**) allows for a single dose ( $1.5 \times 10^{11}$  vector genomes) per eligible eye, per lifetime in beneficiaries who meet all of the coverage indications and documentation requirements as outlined in this LCD. Additionally, coverage is limited to manufacturer-designated Centers of Excellence with expertise in heritable retinal degenerations when performed by qualified vitreoretinal surgeons with evidence of completion of the manufacturer's surgical and pharmacy training program for the appropriate storage, handling, and administration of voretigene neparvovec-rzyl (**LUXTURNA®**).

*(The above Medicare information is current as of the review date for this policy. However, the coverage issues and policies maintained by the Centers for Medicare & Medicare Services [CMS, formerly HCFA] are updated and/or revised periodically. Therefore, the most current CMS information may not be contained in this document. For the most current information, the reader should contact an official Medicare source.)*

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## Related Policies

- Genetic Testing and Counseling
  - Luxturna™ (voretigene neparvovec-rzyl)—Pharmacy policy
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*The articles reviewed in this research include those obtained in an Internet based literature search for relevant medical references through March 2023 the date the research was completed.*

### Joint BCBSM/BCN Medical Policy History

Policy Effective Date	BCBSM Signature Date	BCN Signature Date	Comments
9/1/16	6/21/16	6/21/16	Joint policy established
3/1/17	12/13/16	12/13/16	Code 81434 added to policy. Updated clinical trial information.
7/1/18	4/17/18	4/17/18	Policy statement addition: Genetic testing in patients with retinal dystrophy for biallelic RPE65 mutation is established in patients who are eligible for Voretigene Neparvovec-rzyl also known as SPK-RPE65 gene therapy. Inclusions-pharmacy criteria on Luxturna added. Updated rationale, added reference 20 & 21. Code 81406 now established.
7/1/19	4/16/19		Routine policy maintenance. No change in policy status.
7/1/20	4/14/20		Routine policy maintenance. No change in policy status.
7/1/21	4/20/21		Routine policy maintenance. CMS section updated. No change in policy status.
7/1/22	4/19/22		Routine policy maintenance, no change in policy status.
7/1/23	4/18/23		Routine policy maintenance, no change in policy status. Vendor managed: N/A. (ds)

Next Review Date: 2<sup>nd</sup> Qtr. 2024

### Pre-Consolidation Medical Policy History

Original Policy Date	Comments
BCN:	Revised:
BCBSM:	Revised:





**BLUE CARE NETWORK BENEFIT COVERAGE  
POLICY: GENETIC TESTING FOR RETINAL DYSTROPHIES**

**I. Coverage Determination:**

<b>Commercial HMO (includes Self-Funded groups unless otherwise specified)</b>	Covered per policy guidelines
<b>BCNA (Medicare Advantage)</b>	See government section.
<b>BCN65 (Medicare Complementary)</b>	Coinsurance covered if primary Medicare covers the service.

**II. Administrative Guidelines:**

- The member's contract must be active at the time the service is rendered.
- Coverage is based on each member's certificate and is not guaranteed. Please consult the individual member's certificate for details. Additional information regarding coverage or benefits may also be obtained through customer or provider inquiry services at BCN.
- The service must be authorized by the member's PCP except for Self-Referral Option (SRO) members seeking Tier 2 coverage.
- Services must be performed by a BCN-contracted provider, if available, except for Self-Referral Option (SRO) members seeking Tier 2 coverage.
- Payment is based on BCN payment rules, individual certificate and certificate riders.
- Appropriate copayments will apply. Refer to certificate and applicable riders for detailed information.
- CPT - HCPCS codes are used for descriptive purposes only and are not a guarantee of coverage.